Clinical Research Trial

The University of Utah
School of Medicine

For Female Adolescents with Depression

What is the study about?

An investigational drug is being tested to see if it reduces symptoms in females with Major Depression who have not responded to Prozac® (Fluoxetine) or Lexapro®. Magnetic Resonance Imaging Spectroscopy (MRI/MRS) brain scans will be performed in addition to standard clinical assessments.

What are the benefits of participation?

- Participants receive a comprehensive medical and psychiatric evaluation.
- Treatment with the investigational drug at no cost.
- MRI scans at no cost. Participants can keep a copy if they want.
- Participants may stay on their current medications during the study.

Who can enroll in the study?

- Participants must have a diagnosis of Major Depressive Disorder, and must be currently taking Fluoxetine (Prozac®).
- Participants must be females between the ages of 13-17 years.

What do I have to do if I or my child is in the study?

- Participants attend 1 screening visit and 6 treatment visits in a 10-week period.
- Before starting treatment, participants are required to have testing for pregnancy and drugs of abuse, in addition to regular labs to ensure they are generally in good health.
- Participants will have 2 MRI scans: one at the beginning, and after 6 weeks of treatment.

What is the study called?

"Adjunctive Creatine Treatment for Adolescent Females with Major Depressive Disorder who are Non-Responders to Fluoxetine: A Magnetic Resonance Spectroscopy Study."

Compensation Will be Provided to Study Participants.

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Creatine Depression Study
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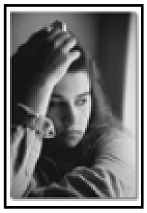
Clinical Research Trial

The University of Utah
School of Medicine

For Depressed Adolescents with Bipolar Disorder



What is the study about?

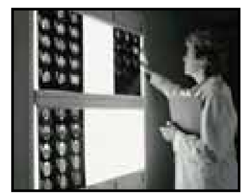
An investigational drug is being tested to see if it reduces depression symptoms in adolescents with Bipolar Disorder. Magnetic Resonance Imaging Spectroscopy (MRI/MRS) brain scans will be performed in addition to standard clinical assessments. The study is sponsored by the National Institutes of Health.

What are the benefits of participation?

- Participants receive a comprehensive medical and psychiatric evaluation.
- Treatment with the investigational drug at no cost.
- MRI scans at no cost. Participants can keep a copy if they want.
- Participants may stay on their current medications during the study.

Who can enroll in the study?

- Participants must have a diagnosis of Bipolar Disorder, and current depressive symptoms for 2 weeks.
- Males and females 13-18 years old.
- Participants must be on stable dose of their current medications for 2 weeks when they enter the study. ***Patients not on medication for Bipolar Disorder may also enroll with parents' consent.***



What do I have to do if I or my child is in the study?

- Participants attend 2 screening visits and 8 treatment visits in a 12-week period.
- Before starting treatment, participants are required to have testing for pregnancy and drugs of abuse, in addition to regular labs to ensure they are generally in good health.
- Participants will have 2 MRI scans: one at the beginning, and after 6 weeks of treatment.

What is the study called?

"Oral administration of uridine for treatment of bipolar depression in adolescents: a magnetic resonance spectroscopy study." Uridine is a member of a family of compounds called nucleosides that occur naturally in the human body.

Compensation will be provided to study participants.

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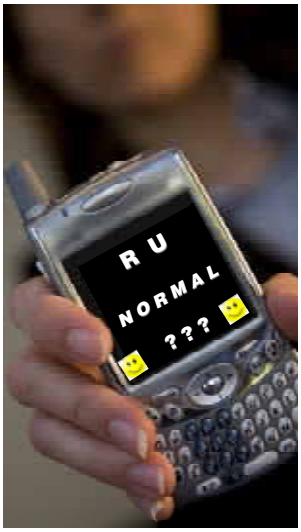


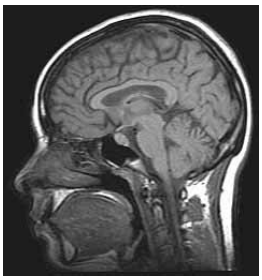
The University of Utah
School of Medicine

CLINICAL RESEARCH STUDY

Recruiting Healthy Adolescents Aged 13-17

What is the study about?

An investigational drug is being tested to see if it reduces depression symptoms in adolescents with Bipolar Disorder. Magnetic Resonance Imaging (MRI) brain scans will be performed. The researchers will compare the brain scans of healthy adolescents with the MRI scans of adolescents with Bipolar Disorder. The study is sponsored by the U.S. National Institute of Health.



What are the benefits of participation?

- Participants receive a medical and psychiatric evaluation by a physician.
- Two MRI brain scans at no cost. Participants can keep a copy if they want.
- Healthy adolescents are not asked to take study medication.

Who can enroll in the study?

- Males and females 13-17 years old in good health.
- Participants must not have Depression, Bipolar Disorder, ADHD, Schizophrenia, Drug Addiction or Claustrophobia (a fear of enclosed spaces).

What do I have to do if I or my child is in the study?

- Participants will attend two visits approximately 6 weeks apart.
- Participants will have urine tests for pregnancy and drug abuse.
- Healthy participants will not have blood draws or take medication.
- Participants have one MRI brain scan when they enroll and a second scan 6 weeks later.

What is the study called?

"Oral administration of uridine for treatment of bipolar depression in adolescents: a magnetic resonance spectroscopy study."

COMPENSATION WILL BE PROVIDED TO STUDY PARTICIPANTS

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Pediatric Bipolar Disorder & Suicide

Douglas Kondo, M.D.

University of Utah Brain Institute

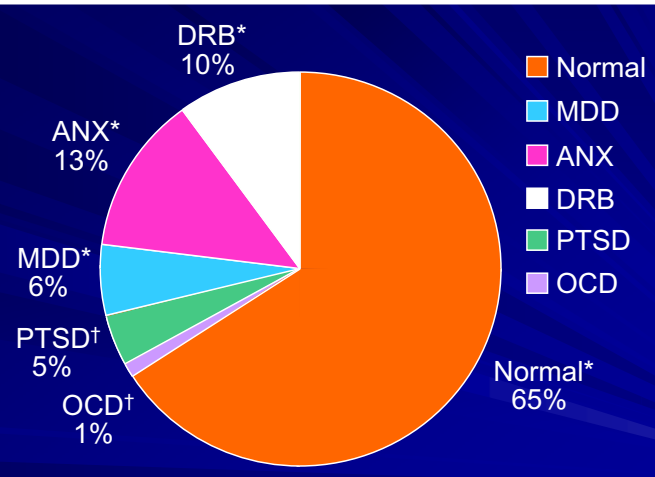
Child & Adolescent Psychiatry Trials Network

Duke Clinical Research Institute

Disclosures & Conflict of Interest Statement

Nothing to disclose.

Psychiatric Disorders in Youth



* Shaffer D et al. (1996) *J Am Acad Child Adolesc Psychiatry*, 35:865-877.

† Costello EJ, Angold A. Epidemiology. (1995) In: J March, ed. *Anxiety Disorders in Children and Adolescents*. New York: Guilford Press.

Overview

- **Pediatric Bipolar Disorder**
  - Epidemiology
  - Diagnosis
  - Treatment
- **Adolescent Suicide**
  - Overview of the Literature
  - Utah Youth Suicide Study
- **Research at the University of Utah**

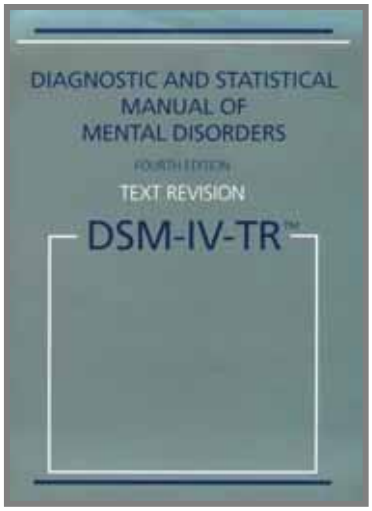
Pediatric Bipolar Spectrum Disorders

- Less well studied than in adults
- Diagnosis possible in young children using DSM criteria
- Poor overall functioning, academic failure, legal difficulties, multiple hospitalizations, substance abuse, suicide attempts and completions

Pediatric Bipolar Spectrum Disorders

- Presentation differs in children and adolescents
- Continuous, daily cycling seen in a substantial number of children & adolescents (Geller et al., 1995, 2000, 2002)
- Multiple daily "mood swings" and baseline irritability may be more common than classic euphoria in youth with bipolar disorders

Diagnostic and Statistical Manual (DSM-IV-TR)



DSM-IV-TR criteria for a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1. inflated self-esteem or grandiosity
2. decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
3. more talkative than usual or pressure to keep talking
4. flight of ideas or subjective experience that thoughts are racing
5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
6. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
7. excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

DSM-IV-TR criteria for a Hypomanic Episode

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual non-depressed mood.

B. **During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree**:

1. inflated self-esteem or grandiosity
2. decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
3. more talkative than usual or pressure to keep talking
4. flight of ideas or subjective experience that thoughts are racing
5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
6. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
7. excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

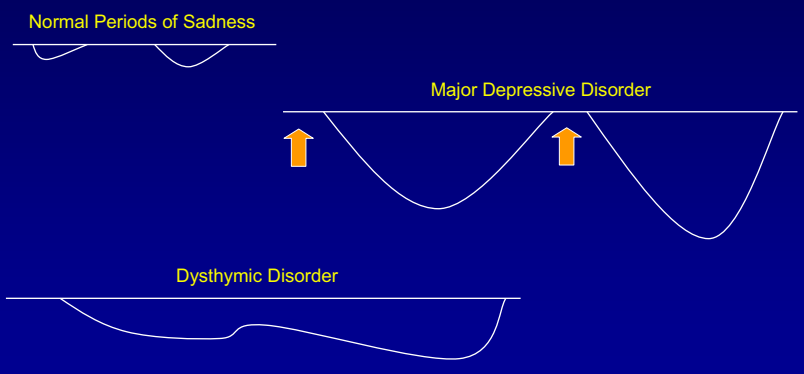
DSM-IV-TR Criteria for a Mixed Episode

A. The criteria are met both for a Manic Episode and for a Major Depressive Episode nearly every day during at least a 1-week period.

B. The mood disturbance is sufficiently severe to cause impairment in occupational functioning or in social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

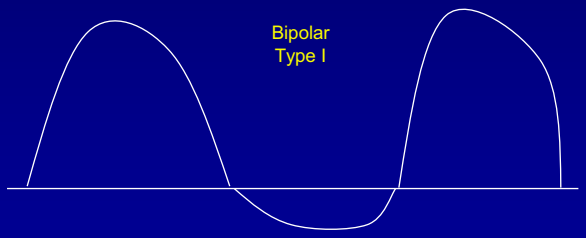
C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Patterns of DSM-IV-TR Mood Disorders

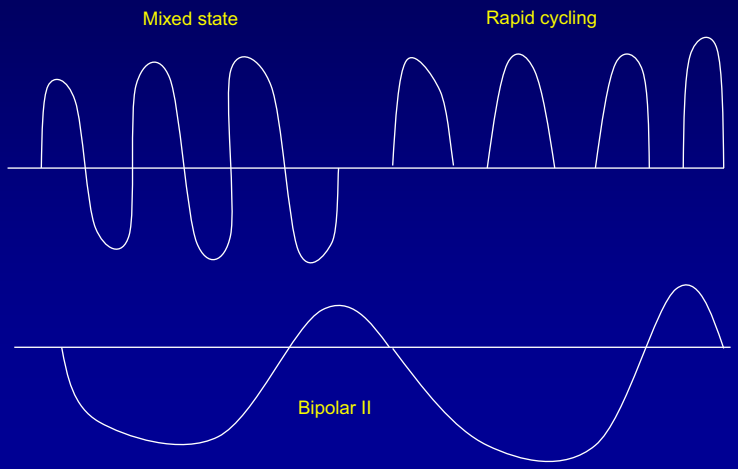


Patterns of mood disorders

Normal periods of happiness



Patterns of mood disorders



Epidemiology

Prevalence of BP in Adolescents

Diagnostic interviews with 1709 high school students, ages 14-18 years

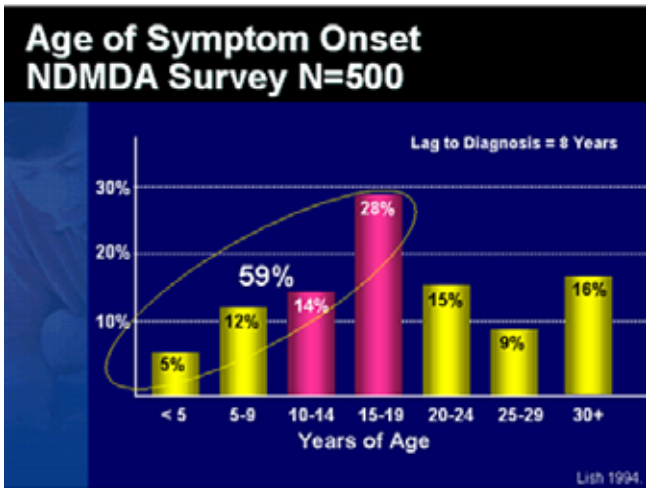
Findings

1.0% prevalence of BP (primarily BP II and cyclothymia)

5.7% prevalence of BP NOS

Lewinsohn 1995

Age of Onset: Pediatric Bipolar Disorder



Characteristics of Bipolar Disorder in Youth

- 93 Outpatients: 7 - 16 years with Bipolar Disorder Type I or II
- Average age = 11 years
- Mean age at onset 7 y/o
- Mean episode duration 3.5 years

Symptoms	Percentage of Patients
Mixed Mania	55%
Rapid Cycling	87%
Grandiose Delusions	50%
Suicidality	25%
Co-morbid ADHD	87%

Geller et al., 2000

Common Presenting Symptoms

- Episodes of depression with hopelessness
- Excessive mood lability
- Periods of increased or decreased energy
- Episodes of decreased need for sleep
- Anger and affect dysregulation
- Marked irritability
- Frequently argumentative
- Bold / Intrusive / Demanding Behaviors
- Hypersexuality

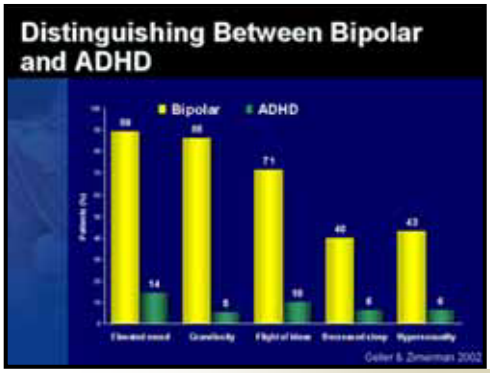
Bipolar Disorder vs. ADHD

Bipolar Disorder > ADHD

- Elevated Mood
- Grandiosity
- Hypersexuality
- Decreased Sleep
- Racing Thoughts
- Cycling

Bipolar Disorder = ADHD

- Distractibility
- Hyperactivity
- Irritability

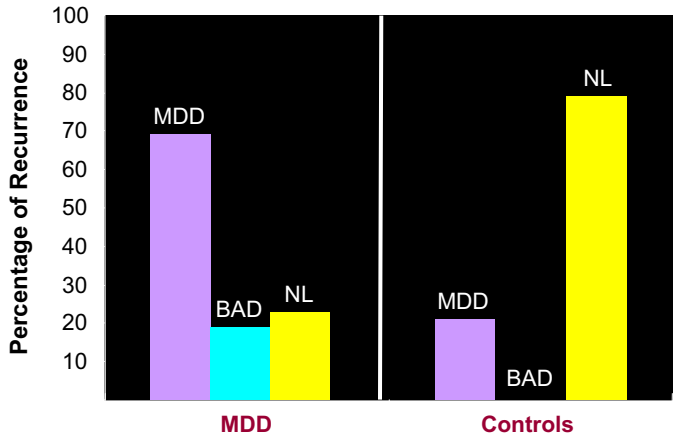


Diagnostic Evaluation

- **For Research Studies:**
  - WASH-U-KSADS
    - Can take up to 4 hours
- **For Busy Clinicians:**
  - Thorough History & Interview (child/parents)
  - ***FAMILY HISTORY* is key**!
  - Communicate with the School
  - Obtain Collateral Information
  - Parent – Young Mania Rating Scale (YMRS-P)
  - Child Mania Rating Scale (CMRS)

7-Year Follow-Up of Depressive Episode

Rao et al. *J Am Acad Child Adolesc Psychiatry* (1995) 34:566-578.



MDD = Major Depression **BAD = Bipolar Disorder** **NL = Normal**

Average Age of Onset

- **Major Depressive Disorder**
  - Epidemiologic Catchment Area Study: 25.6 years
  - National Comorbidity Survey: 23.8 years
- **Bipolar Disorder**
  - Epidemiologic Catchement Area Study: 18.1 years
  - National Comorbidity Survey: 21.0 years

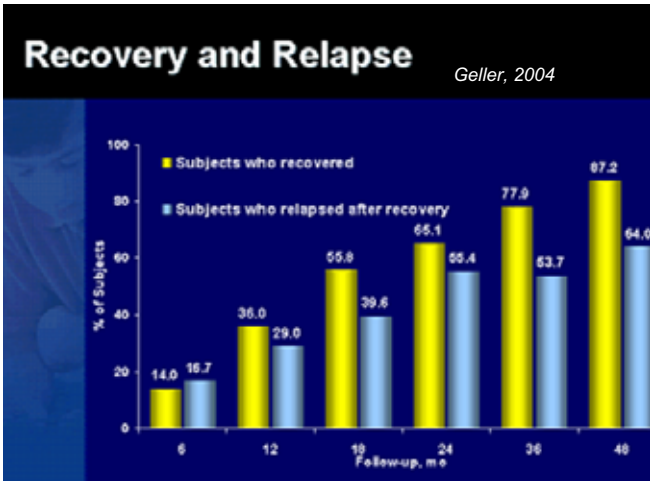
ECA 1980; NCS 1990

Stanley Foundation Bipolar Network: *Age at Onset*

- 480 patients with Bipolar Disorder
- 14% experienced onset in childhood (≤12 years)
- 35% onset in adolescence (13 to 18 years)
- 51% onset in adulthood
- Early-onset bipolar illness was associated with significant delay to first treatment, averaging more than 16 years (!)

Leverich, G.S. et al. (2007) The Journal of Pediatrics (150)5:485-90.

Pediatric Bipolar Disorder – Course and Outcome



Biederman (2005): 90% of Bipolar Children Failed to Attain Euthymia Over a 10-year Period

Pediatric Bipolar Disorder: FDA-Approved Medications

- **Aripiprazole (Abilify™)**
  - Age 10-17 years — Bipolar Disorder
- **Risperidone (Risperdal™)**
  - Age 5-16 years — Autism
  - Age 10-17 years — Bipolar Disorder
- **Olanzapine (Zyprexa)**
  - Age 13-17 years — Bipolar Disorder
- **Lithium**
  - Age ≥ 12 years — Bipolar Disorder

Pediatric Suicidal Behavior

Adolescent Suicide & Attempts: a Major Public Health Problem

- **Suicide is the 3rd leading cause of death for 10- to 24-year-olds in the U.S.**
- **Suicide among 15- to 19-year-olds accounts for a greater number of deaths than the next 7 leading causes of death combined**
- **Suicide attempts are a leading reason for emergency room visits, and psychiatric hospitalizations**
- **Adolescent suicide attempts are associated with increased risk of both subsequent non-lethal suicidal behavior and death by suicide**
- **Males commit 75% of suicides; twice as many females attempt suicide**

Suicide: Defining the Terms

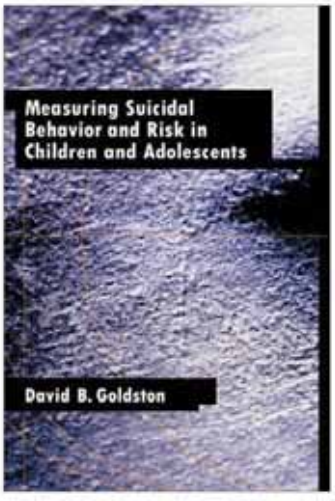
- **SUICIDE: Death from injury, poisoning, or suffocation where there is evidence that the injury was self-inflicted, and that the decedent intended to die.**
- **SUICIDE ATTEMPT: A potentially self-injurious behavior with a non-fatal outcome, for which there is evidence (either explicit of implicit) that the person intended at some (non-zero) level to kill him or herself.**
  - *N.B. A suicide attempt may – or may not – result in injuries.*

(O'Carroll et al., 1996)

Adolescent Suicidality: Assessment

- Detection Instruments: Suicide Behaviors Questionnaire, Suicide Ideation Questionnaire, Beck Suicide Ideation Inventory
- Risk Assessment Instruments: Beck Hopelessness Scale, Child Hopelessness Scale
- Assessing the Clinical Characteristics of Suicidal Behavior: Beck Suicide Intent Scale, Lethality of Suicide Attempt Rating Scale
- Assessment of Suicidal Behavior in Clinical Trials: Columbia Suicide Severity Scale

Assessment of Youth Suicidality



U.S. Rates: Adolescent Completed Suicide, Attempts & Ideation (2007)

Adolescent Suicide Rate (Age 15-19 years) (CDC) – 3rd leading cause of death	8.0/100,000
High School Students Seriously Considering Suicide (YRBSS 2007)	15%
High School Students Making a Specific Suicide Plan (YRBSS 2007)	11%
High School Students Who Attempted Suicide at Least Once in Past 12 Months (YRBSS 2007)	7%
High School Students Requiring Treatment for a Suicide Attempt (YRBSS 2007)	2%

Risk Factors for Adolescent Suicide

- **Mood disorder and/or substance abuse disorder**
- **History of physical and/or sexual abuse**
- **History of prior attempt(s)**
- **Living in a less-densely populated area**
- **Access to firearms**

Prevention

Key Points

- **Suicide is rare and thus hard to predict**
- **Between 25-50% of patients with Bipolar Disorder attempt suicide at least once**
- **Only one medication – Lithium – is proven to reduce the rate of suicide in Bipolar Disorder**

Warning Signs

- **Talking about suicide**
- **Frequently thinking or talking about death**
- **Comments about feeling hopeless, helpless, or worthless**
- **Statements like "It would be better if I wasn't here"**
- **Worsening depression**
- **A sudden switch from being sad to being calm or appearing to be happy**
- **Losing interest in things one used to care about**

Effective Suicide Prevention

1. Applying interventions to encourage care-seeking by patients at times of distress
2. Problem-solving skills training
3. Combining interventions that include problem solving with rehearsal of cognitive, social, emotion-labeling, and distress-tolerance skills

(Gray & Otto, 2001)

Child Psychiatry Research at the University of Utah

1) Complementary & Alternative Medicine (CAM) Treatments

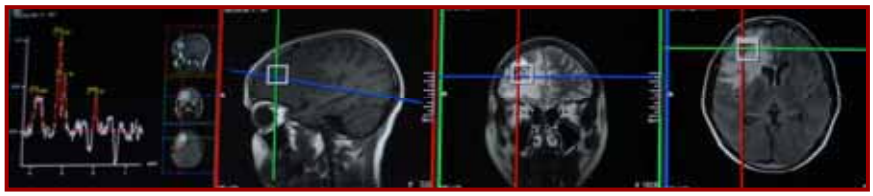
2) Neuroimaging to Investigate the Underlying Biochemistry of Mood Disorders

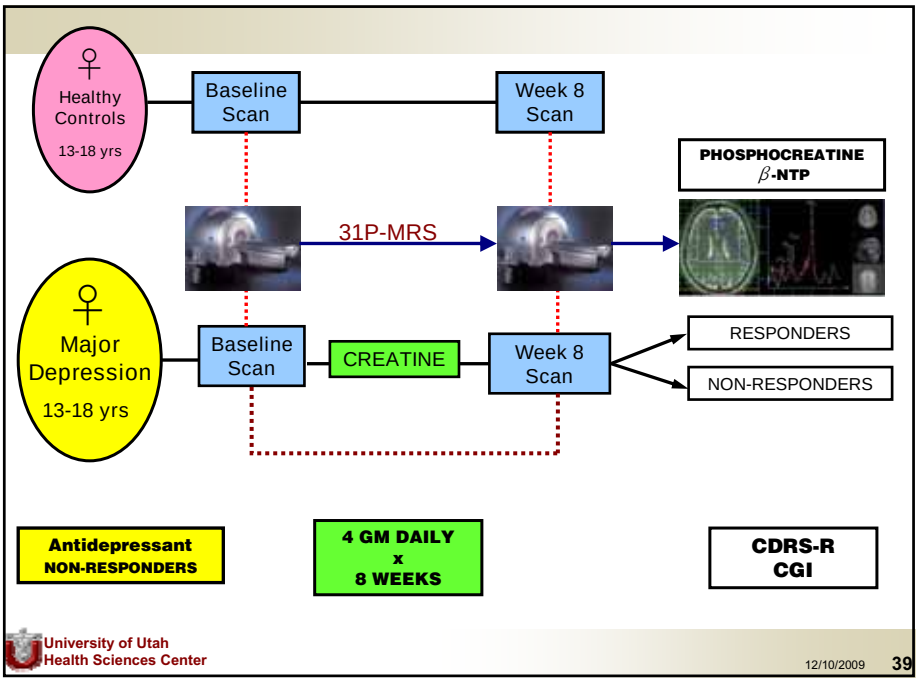
3) The Utah Youth Suicide Study

Magnetic Resonance Spectroscopy Facility

University of Utah Center for Advanced Medical Technologies

→ *Utah Center for Advanced Imaging Research (UCAIR)*





Questions & Discussion

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